*British Heart Journal*, 1975, 37, 656–661.

# Aortic stenosis, angina, and coronary artery disease *Interrelations*

Clifford N. Harris, Marvin A. Kaplan, David P. Parker, Edward F. Dunne, H. Stanley Cowell, and Myrvin H. Ellestad

*From the Los Angeles Heart Institute, St. Vincent Medical Center, Los Angeles, California; the Cardiology Section, Medical Services, Veterans Administration Hospital, Long Beach, California; the University of California, Irvine, California; and the Memorial Hospital Medical Center of Long Beach, California, U.S.A.*

*Sixty-nine patients over age 35 with severe valvular aortic stenosis were investigated for concomitant coronary artery disease. Forty (57.9%) had clinical angina pectoris. Sixteen (23.2%) had significant coronary occlusive disease by arteriography. Of those with angina, 13 patients (32.5%) had significant coronary arterial obstruction, while in the pain-free group only 3 (10.3%) had occlusive coronary disease. It is concluded that patients with severe aortic stenosis who are free of angina have only a small, but definite, chance of having significant coronary disease.*

It has become the practice in many institutions over the past several years to perform coronary arteriography on all patients with valvular aortic stenosis who are to undergo valve replacement surgery. The rationale for this is twofold: 1) to evaluate coronary arterial patency in planning for cannulation and perfusion during extracorporeal bypass, and 2) to delineate the extent and severity of coronary arteriosclerosis as a prognostic guideline and preparatory to potential coronary arterial bypass by saphenous vein graft at the time of valve surgery.

The prognostic import of concomitant coronary atherosclerosis in patients being operated upon for aortic stenosis has been pointed out by numerous authors (Elliott *et al.*, 1964; Peterson *et al.*, 1967; Linhart and Wheat, 1967). The feasibility and desirability of performing coronary bypass surgery in appropriate patients at the time of aortic valve replacement has been discussed by Loop and coworkers (1972). Moreover, in many institutions coronary bypass can be performed where indicated at the time of aortic valve replacement without significantly increasing the surgical risk. It would, therefore, be advantageous if some clinical indicator could be identified which would predict the presence or absence of coronary artery disease in aortic stenosis patients with a degree of surety. Because it seemed that the presence or absence of angina pectoris might, in such patients, provide a differential clue, we undertook the present investigation.

Received 8 January 1975.

## Subjects and methods

Cardiac catheterization laboratory records were reviewed to identify all patients who had undergone both diagnostic catheterization for evaluation of aortic stenosis and coronary arteriography from the date it became routine policy in our hospitals to perform the latter procedure on all cases of left ventricular outflow obstruction before surgery. Since we were interested in examining only those patients with unequivocally severe aortic stenosis who were in an age range which could make concomitant coronary atherosclerosis a reasonable possibility, the following criteria were established for inclusion in the study: 1) A systolic aortic valvular gradient of more than 50 mmHg (6.7 kPa) or calculated aortic valve area of less than 0.75 $cm^2$, and 2) age over 35 years. Several patients included in the study had associated trivial aortic regurgitation or mitral valve disease, but in all cases aortic stenosis was clearly the dominant lesion. Aortic valve areas were calculated by the hydraulic formula of Gorlin and Gorlin (1951), where applicable. Four patients were included in whom the aortic valve could not be traversed at the time of catheterization but in whom the presence of severe aortic stenosis was confirmed at surgery.

Selective coronary arteriography was performed by the Sones' or Judkin's technique. In the majority of cases, the coronary arteries were opacified in at least two views, usually the left and right anterior oblique. An occasional case was retained in which a vessel was seen in one

projection only but was obviously either widely patent or narrowed. In 3 cases in this latter group, one of the coronary vessels was clearly opacified by aortic root angiogram rather than by selective ostial injection. The arteriograms were reviewed independently by 3 of the authors who had no knowledge of the clinical details. Films of poor quality were rejected from the study. Each coronary artery was graded from 0 to 100 per cent in terms of the maximum degree of obstruction of the most severe narrowing of that vessel. It was arbitrarily decided to accept a stenosis of 75 per cent or greater as evidence of significant coronary artery disease. Where the reviewers differed by more than 25 per cent in their assessment of severity of a given lesion, a joint viewing was made and a concensus reached.

All patients included in the study by the above criteria were then assessed for the presence of angina pectoris. Angina was diagnosed by the usual clinical criteria, either by one of the authors personally or by the responsible physician. Results were analysed for statistical significance by means of a t-test where mean values were compared or Fisher's exact test otherwise.

## Results

Results are shown in Tables 1 to 4. Of our 69 patients, 16 (23.2%) had significant coronary artery disease; 40 (57.9%) had angina pectoris, and 13 within this group (32.5%) had significant coronary artery disease. Twenty-nine patients did not complain of angina and only 3 of these patients (10.3%) were found to have a significant obstructing coronary lesion. The difference in prevalence of coronary disease between these two groups was statistically significant ($P < 0.05$). The mean age of the patients with angina was 59.5 years while that of those without angina was 56.6 years. The mean gradient across the aortic valve in the former group was 82.7 mmHg (11.0 kPa); that in the latter group was 79.9 mmHg (10.6 kPa). The differences between the mean ages and gradients of the two groups were not statistically significant ($P > 0.05$).

Those patients with angina were subdivided into two groups depending upon the presence or absence of coronary artery disease. There were 27 patients without significant coronary arterial obstruction. The mean age of this group was 57.6 years and the mean gradient across the aortic valve was 86 mmHg (11.4 kPa). There were 13 people who had significant coronary arterial obstruction among those with angina. The mean age of these 13 was 63.4 years and the mean gradient across the aortic valve was 75.8 mmHg (10.1 kPa). The age difference between these two groups was of borderline statistical significance ($P < 0.10$). The difference in mean gradient was not statistically significant ($P > 0.05$).

The patients without angina were also broken down into a group of 26 without coronary artery disease and a group of 3 with obstructive arterial lesions. The mean age and gradient in the former group were 55.7 years and 80.5 mmHg (10.7 kPa), respectively. In the latter group the comparable figures were 64.6 years and 75 mmHg (10.0 kPa). The differences between the mean age and gradients of the two groups were not statistically significant ($P > 0.05$).

## Discussion

Angina pectoris has long been recognized as a prominent symptom in patients with valvular aortic stenosis. There are many reasons for this relation, and a consideration of the physiological principles governing coronary flow (Gorlin, 1966) makes many of them clear. Among the major factors, abnormal flow patterns (Levine, 1945) across a diseased aortic valve, presumably interfering with coronary filling, coupled with the increased oxygen needs of a myocardium overburdened by hypertrophy and increased systolic wall tension, result in myocardial ischaemia and its frequent clinical counterpart, angina. Recently, it has been shown experimentally in animals and in humans (Vincent, Buckberg, and Hoffman, 1974) that with increasing degrees of aortic constriction, despite an increase in mean coronary blood flow, flow in diastole falls conspicuously. When this occurs, left ventricular myocardial blood flow becomes inhomogeneous, with a significant decrease in the proportion of flow to the subendocardial muscle. This mechanism has been suggested as an explanation for ischaemia in the hypertrophied left ventricle, even in the presence of a normal coronary arterial tree.

Since severe aortic stenosis in adults is most commonly found within an age range which is virtually identical to that containing the majority of patients with arteriosclerotic heart disease, the overlap and interrelations of these two diseases have been extensively commented on in the past. Some early studies (Zeek, 1932), suggested that the rheumatic process might accelerate atherosclerosis. These were followed by pathological correlations (Horan and Barnes, 1948; Anderson, Kelsey, and Edwards, 1952; Nakib, Lillehei, and Edwards, 1965; Dry and Willius, 1939) reporting an inverse relation between degree of aortic valvular obstruction and degree of coronary atherosclerosis, and implying a 'protective' effect of some sort by aortic stenosis on the coronary vasculature. More recent studies (Elliott *et al.*, 1964; Linhart and Wheat, 1967; Coleman and Soloff, 1970; Linhart *et al.*, 1968) have denied the concept of protection, showing that coronary artery disease is a frequent concomitant of aortic stenosis and an important determinant of the

future course of many patients. Linhart and co-workers (1968) go so far as to recommend that 'the coronary vessels should be evaluated in every patient prior to aortic valve replacement'.

Before our data or hypotheses can be properly interpreted, several aspects of our methods must be examined. Most importantly, our study is in large part retrospective and, therefore, is affected by the problems inherent in that approach. It should also be noted that the large majority of the patients included in our study were men. This is, of course, primarily a reflection of the patient population of the Veterans Administration Hospital which contributed a substantial portion of our case material.

Finally, it might be pointed out that our study population was not a very large one, making it more difficult to draw accurate conclusions. The series is unselected, however, in that it represents all older

TABLE I *Patients with angina*

| *Case No.* | *Age (yr)* | *Peak aortic valve gradient (kPa)* | *Coronary arteries* | | | |
|---|---|---|---|---|---|---|
| | | | *Left main* | *Left anterior descending* | *Circumflex* | *Right* |
| 1 | 48 | 10 | Nl | 100% | Nl | Nl |
| 2 | 55 | 7.3 | Nl | 100% | Nl | Nl |
| 3 | 50 | 10.8 | Nl | 95% | Nl | Nl |
| 4 | 46 | 10.5 | Nl | Nl | Nl | Nl |
| 5 | 50 | 9.0 | Nl | Nl | Nl | Nl |
| 6 | 56 | 12.0 | Nl | Nl | Nl | Nl |
| 7 | 77 | 12.9 | Nl | Nl | Nl | Nl |
| 8 | 63 | 8.4 | Nl | Nl | 90% | 90% |
| 9 | 66 | 7.3 | Nl | Nl | Nl | Nl |
| 10 | 56 | 5.2 (valve area = 0.60 $cm^2$) | Nl | 60% | 100% | 95% |
| 11 | 68 | 10.9 | Nl | Nl | Nl | 90% |
| 12 | 56 | 11.7 | Nl | Nl | Nl | Nl |
| 13 | 69 (F) | 17.3 | Nl | Nl | Nl | Nl |
| 14 | 70 | 10.5 | Nl | 80% | Nl | 50% |
| 15 | 67 (F) | 12.2 | Nl | Nl | Nl | Nl |
| 16 | 76 | 13.3 | Nl | Nl | Nl | Nl |
| 17 | 47 | 9.3 | Nl | 40% | Nl | Nl |
| 18 | 47 | 13.3 | Nl | Nl | Nl | Nl |
| 19 | 69 (F) | 17.3 | 80% | Nl | Nl | Nl |
| 20 | 55 (F) | 15.7 | Nl | Nl | Nl | 40% |
| 21 | 41 | 9.3 | Nl | Nl | Nl | Nl |
| 22 | 48 | 9.3 | Nl | 40% | Nl | Nl |
| 23 | 58 | 11.2 | Nl | Nl | Nl | 50% |
| 24 | 61 (F) | 12.0 | Nl | Nl | Nl | Nl |
| 25 | 51 | 12.5 | Nl | Nl | Nl | Nl |
| 26 | 59 | 8.8 | Nl | Nl | Nl | Nl |
| 27 | 62 (F) | * Not measured | Nl | Nl | Nl | Nl |
| 28 | 49 | 9.3 | Nl | Nl | Nl | Nl |
| 29 | 62 | 9.6 | Nl | 100% | 90% | 80%† |
| 30 | 66 | * Not measured | Nl | Nl | Nl | Nl |
| 31 | 61 | 16.6 | Nl | Nl | 50% | 70% |
| 32 | 64 (F) | 8.0 | Nl | Nl | Nl | Nl |
| 33 | 48 | 9.3 | Nl | 40% | Nl | Nl |
| 34 | 74 | * Not measured | Nl | 80% | Nl | Nl |
| 35 | 58 | 11.2 | Nl | Nl | Nl | 50% |
| 36 | 65 | 14.6 | Nl | Nl | Nl | Nl |
| 37 | 70 (F) | 9.3 | Nl | 100% | Nl | Nl |
| 38 | 63 | 7.2 | Nl | 100% | Nl | Nl |
| 39 | 53 | 9.3 | Nl | Nl | Nl | Nl |
| 40 | 76 | 14.6 | Nl | 50% | 90% | 70% |

* – Confirmed at surgery as severe aortic stenosis.
† – Percentage obtained at necropsy.
F – Female.
Nl – Normal.
*Conversion factor from SI units to Traditional units:* 1 kPa ≈ 7.5 mmHg.

TABLE 2 *Patients without angina*

| *Case No.* | *Age (yr)* | *Peak aortic valve gradient (kPa)* | *Coronary arteries* | | | |
|---|---|---|---|---|---|---|
| | | | *Left main* | *Left anterior descending* | *Circumflex* | *Right* |
| 41 | 58 | 13.3 | Nl | 60% | 75% | Nl |
| 42 | 48 | 16.0 | Nl | Nl | Nl | Nl |
| 43 | 66 | 12.2 | Nl | Nl | Nl | 25% |
| 44 | 38 | 8.9 | Nl | Nl | Nl | 30% |
| 45 | 48 | 16.4 | Nl | Nl | Nl | Nl |
| 46 | 62 | 10.6 | Nl | Nl | Nl | Nl |
| 47 | 59 | 12.8 | Nl | Nl | Nl | Nl |
| 48 | 56 | 7.8 | Nl | Nl | Nl | Nl |
| 49 | 47 | 6.1 (valve area = 0.45 $cm^2$) | Nl | Nl | Nl | Nl |
| 50 | 58 | 12.1 | Nl | Nl | Nl | Nl |
| 51 | 58 | 8.0 | Nl | Nl | Nl | Nl |
| 52 | 60 | * Not measured | Nl | Nl | Nl | Nl |
| 53 | 77 | 5.3 (valve area = 0.5 $cm^2$) | Nl | Nl | Nl | Nl |
| 54 | 67 | 6.7 | Nl | 40% | Nl | 75% |
| 55 | 39 | 13.0 | Nl | Nl | Nl | Nl |
| 56 | 51 | 10.0 | Nl | Nl | Nl | Nl |
| 57 | 69 (F) | 9.3 | Nl | Nl | Nl | Nl |
| 58 | 51 | 10.0 | Nl | Nl | Nl | Nl |
| 59 | 51 | 11.2 | Nl | Nl | Nl | Nl |
| 60 | 48 | 17.3 | Nl | Nl | Nl | Nl |
| 61 | 63 (F) | 12.8 | Nl | Nl | Nl | Nl |
| 62 | 64 | 7.2 | Nl | Nl | Nl | Nl |
| 63 | 69 | 10.0 | Nl | 60% | Diffuse | 90% |
| 64 | 54 | 7.3 | Nl | Nl | Nl | Nl |
| 65 | 52 | 8.0 | Nl | 50% | Nl | Nl |
| 66 | 67 (F) | * Not measured | Nl | Nl | Nl | Nl |
| 67 | 45 | 8.2 | Nl | Nl | Nl | Nl |
| 68 | 56 | 12.0 | Nl | Nl | Nl | Nl |
| 69 | 60 | 14.4 | Nl | Nl | Nl | Nl |

* – Confirmed at surgery as severe aortic stenosis.
F – Female.
Nl – normal.
*Conversion factor from SI units to Traditional units:* 1 kPa $\approx$ 7.5 mmHg.

patients with severe aortic stenosis seen at our several institutions since coronary arteriography became a routine procedure for evaluation of such individuals. Moreover, the statistical analysis of our data suggests that the differences we found were real rather than chance ones. It seems, therefore, that the relatively small number involved should not invalidate our findings.

Our results indicate that 23.2 per cent of an unselected series of older patients with severe aortic stenosis have angiographically demonstrable coronary occlusive disease. Moreover, in 13 of the 16 individuals with such disease, the significant lesions were confined to a single vessel. These are figures suggesting limited involvement, and stand in contrast to the conclusions of Linhart *et al.* (1968). We have no ready explanation for the differences between our findings and those of this other group cited above. However, determining whether our aortic stenosis patients have much more or less coronary atherosclerosis than a series of age-matched normals could be predicated on knowledge of the coronary artery anatomy of these controls. This information, for obvious reasons, would be difficult to obtain, and to our knowledge no such series is available for comparison. Contrasting angiographic data with material derived from earlier necropsy studies would also be invalid. Therefore, though our figures suggest a low association of coronary artery disease and aortic stenosis the question of interrelations between these two diseases is debatable. It is clear, however, that the two may certainly coexist with important implications and consequences.

TABLE 3 *Patients with angina*

| | *No.* | *Mean age (yr)* | *Mean gradient (kPa)* |
|---|---|---|---|
| Patients without coronary artery disease | 27 | 57.6 | 11.4 |
| Patients with coronary artery disease | 13 | 63.4 | 10.1 |
| Total | 40 | 59.5 | 11.0 |

*Conversion factor from SI units to Traditional units:* 1 kPa≈7.5 mmHg.

TABLE 4 *Patients without angina*

| | *No.* | *Mean age (yr)* | *Mean gradient (kPa)* |
|---|---|---|---|
| Patients without coronary artery disease | 26 | 55.7 | 10.7 |
| Patients with coronary artery disease | 3 | 64.6 | 10.0 |
| Total | 29 | 56.6 | 10.6 |

*Conversion factor from SI units to Traditional units:* 1 kPa≈7.5 mmHg.

The most important conclusion of our study is that patients with aortic stenosis who are free of angina have approximately a 10 per cent chance of having associated significant coronary artery disease. This finding is in agreement with that reported by Loew, Harken, and Ellis (1972) in a recent analysis of the association of coronary arterial disease in patients with valvular pathology. Thus, while 32.5 per cent of our patients with the symptom of angina pectoris had significant coronary occlusive disease, only 3 of the 29 patients (10.3%) without ischaemic pain had atherosclerotic lesions of any potential importance whatsoever. Moreover, 2 of these 3 patients had lesions, the maximum severity (75%) of which was just at the borderline of what is normally accepted as functional significance and the extent of which was confined to one coronary vessel. By contrast, the majority of patients with angina and obstructive coronary disease had at least one lesion producing luminal compromise of greater than 90 per cent. It seems reasonable to postulate that severe aortic stenosis, with its concurrent increased myocardial oxygen demands, imposes a constant stress on the coronary vasculature. Subendocardial blood flow in particular is considerably decreased in the ventricle with aortic stenosis because of increased diastolic left ventricular intramural pressure (opposing diastolic coronary flow) (Vincent *et al.*, 1974). In the presence of tachycardia induced by exertion, the duration of diastole (time available for perfusion) is also decreased. Thus, a number of factors conducive to subendocardial ischaemia are operative even in the presence of normal coronary vessels. Indeed, studies by Fallen, Elliott, and Gorlin (1967) have shown evidence of ischaemia in the ventricle of patients with aortic stenosis and patent coronary arteries. That even a normal coronary tree may be inadequate to meet these exaggerated demands is also attested to by the identification of individuals with angiographically normal arteries who nevertheless have obvious angina. Presumably also, those patients with a somewhat lesser degree of aortic stenosis who might, under normal circumstances, be pain-free are likely to develop angina with intermediate degrees of coronary atherosclerosis. It is of interest in this regard to note that when patients with angina and coronary artery disease (Table 3) were compared to those with angina who were free of coronary artery disease, the latter group was found to have a mean aortic valve gradient greater than that of the former, though this difference did not achieve statistical significance. Thus, angina developed in those individuals with normal coronary vessels only after their aortic stenosis had reached a higher degree of severity than was required to produce chest pain in patients with pre-existing coronary artery disease. This finding is consistent with the hypothesis presented above. Lastly, it might be assumed by obverse reasoning, that patients with severe aortic stenosis who do not have angina have successfully met the increased demands on their coronary circulation by means of coronary arteries that are physiologically if not anatomically normal: that is, that they have either a normal coronary tree or one with structural lesions which are of little functional

importance. It is possible that our 2 patients without angina who had 75 per cent lesions on angiography may fall into this latter group. A final possibility, of course, is that in some individuals there exists an inability to perceive myocardial ischaemia as chest pain because of a peripheral or central nervous system abnormality. There is, however, no method at present to validate this theory or identify such patients if they exist.

Thus, our analysis has shown that older patients with severe aortic stenosis who are free of angina pectoris have only a small (10%) risk of concomitant important coronary occlusive disease.

The authors acknowledge the help of Ms. Emiko Holmes for the statistical analysis of the results.

## References

Anderson, M. W., Kelsey, J. R., Jr., and Edwards, J. E. (1952). Clinical and pathological considerations in cases of calcific aortic stenosis. *Journal of the American Medical Association*, **149**, 9.

Coleman, E. H., and Soloff, L. A. (1970). Incidence of significant coronary artery disease in rheumatic valvular heart disease. *American Journal of Cardiology*, **25**, 401.

Dry, T. J., and Willius, F. A. (1939). Calcareous disease of the aortic valve; a study of 228 cases. *American Heart Journal*, **17**, 138.

Elliott, W. C., Cohen, L. S., Klein, M. D., Lane, F. J., and Gorlin, R. (1964). Selective cinearteriography study of angina pectoris in valvular heart disease. *Circulation*, **30**, Suppl. III, 73.

Fallen, E. L., Elliott, W. C., and Gorlin, R. (1967). Mechanisms of angina in aortic stenosis. *Circulation*, **36**, 480.

Gorlin, R. (1966). Physiology of the coronary circulation. In *The Heart*. p. 653. Ed. by J. W. Hurst and R. B. Logue. McGraw-Hill, New York City.

Gorlin, R., and Gorlin, S. G. (1951). Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. *American Heart Journal*, **41**, 1.

Horan, M. J., Jr., and Barnes, A. R. (1948). Calcareous aortic stenosis and coronary artery disease. *American Journal of the Medical Sciences*, **215**, 451.

Levine, S. A. (1945). *Clinical Heart Disease*, 3rd ed., p. 44. Saunders, Philadelphia.

Linhart, J. W., De La Torre, A., Ramsey, H. W., and Wheat, M. W., Jr. (1968). The significance of coronary artery disease in aortic valve replacement. *Journal of Thoracic and Cardiovascular Surgery*, **55**, 811.

Linhart, J. W., and Wheat, M. W., Jr. (1967). Myocardial dysfunction following aortic valve replacement. The significance of coronary artery disease. *Journal of Thoracic and Cardiovascular Surgery*, **54**, 259.

Loew, D. E., Harken, D. E., and Ellis, L. B. (1972). Valvular heart disease: undiagnosed valvular involvement, concomitant coronary artery disease and systemic embolization. *American Journal of Cardiology*, **30**, 222.

Loop, F. D., Favaloro, R. G., Shirey, E. K., Groves, L. K., and Effler, D. B. (1972). Surgery for combined valvular and coronary heart disease. *Journal of the American Medical Association*, **220**, 372.

Nakib, A., Lillehei, C. W., and Edwards, J. E. (1965). The degree of coronary atherosclerosis in aortic valvular disease. *Archives of Pathology*, **80**, 517.

Peterson, C. R., Herr, R., Crisera, R. V., Starr, A., Bristow, J. D., and Griswold, H. E. (1967). The failure of hemodynamic improvement after valve replacement surgery. *Annals of Internal Medicine*, **66**, 1.

Vincent, W. R., Buckberg, G. D., and Hoffman, J. I. E. (1974). Left ventricular subendocardial ischemia in severe valvar and supravalvar aortic stenosis. *Circulation*, **49**, 326.

Zeek, P. (1932). Studies in atherosclerosis. I. Conditions in childhood which predispose to the early development of arteriosclerosis. *American Journal of the Medical Sciences*, **184**, 350.

Requests for reprints to Dr. Clifford N. Harris, Cardiology Section, St. Vincent Medical Center, 2131 West Third Street, Los Angeles, California 90057, U.S.A.